DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

93641d

Food and Drug Administration
Center for Devices and
Radiological Health
2098 Gaither Road
Rockville, MD 20850

NOV 7 2002

Via Federal Express
WARNING LETTER

Lynn C. Orfgen
President and CEO
Crittenton Hospital Medical Center
1101 W. University Drive
Rochester, Michigan 48307-1831

Dear Mr. Orfgen:

The purpose of this Warning Letter is to inform you of objectionable conditions found during a Food and Drug Administration (FDA) inspection of your Institutional Review Board (IRB), to discuss the written response to the deviations noted, and to request your prompt response to the remaining issues. The inspection took place during the period of June 20 through 24, 2002, and was conducted by Ms. Alanna Mussawwir-Bias and Ms. Paige E. Wilson, investigators from FDA's Detroit District Office. The purpose of the inspection was to determine whether IRB procedures complied with Title 21, Code of Federal Regulations (21 CFR), Part 50-Protection of Human Subjects, Part 56 – Institutional Review Boards, and Part 812 – Investigational Device Exemptions. These regulations apply to clinical studies of products regulated by the FDA.

Our review of the inspection report submitted by the district office revealed serious violations from pertinent regulations. You received a Form FDA 483, "Inspectional Observations," at the conclusion of the inspection that listed the deviations noted and discussed. We acknowledge receipt of a copy of an August 10 letter from Dale Hoekstra, M.D, the IRB Chair, to Ms. Mussawwir-Bias that includes a description of actions taken in response to items listed on the Form FDA 483. Deviations noted include:

Failure to maintain adequate standard operating procedures (SOPs) governing the functions and operations of the IRB (21 CFR 56.108).

Inspectional review of your SOPs, entitled "Institutional Review Board Plan Crittenton Hospital," revealed a lack of written procedures regarding expedited review, emergency use of investigational products, and determination of appropriate timeframes for continuing review. Inspectional findings also revealed that the IRB approved emergency use of investigational products and expedited approval of studies despite the lack of written procedures.

Failure to provide adequate initial review of investigational studies (21 CFR 56.109(a) and (b)).

There was no documentation that two approved studies reviewed during the inspection received the required full IRB review. Specifically, there is no documentation of a meeting for review and approval of [redacted] product. In addition, IRB records indicate that [redacted] study was approved after review of an investigator brochure that was related to a different study.

Failure to provide adequate continuing review of approved studies (21 CFR 56.109(f)).

The files for six (6) studies reviewed during the inspection lacked evidence that continuing review was performed on at least an annual basis.

Failure to have a quorum of members present when reviewing and approving studies (21 CFR 56.108(c)).

Inspectional findings revealed that at least one study was approved at a meeting at which there was not a quorum of IRB members present.

Failure to maintain meeting minutes in sufficient detail (21 CFR 56.115(a)(2)).

Meeting minutes reviewed failed to include specifics regarding voting on proposed research in that they do not contain the numbers of members voting for, against, and abstaining.

The deviations listed above are not intended to be an all-inclusive list of the deficiencies noted. The IRB is responsible for adhering to each requirement of the law and relevant regulations.

A number of the deviations noted above had been discussed at the previous inspection in 1995. These include inadequate SOPs, deficient continuing review, and incomplete meeting minutes.

Moreover, review of a copy of the IRB SOPs included with the inspection report revealed additional deficiencies, including:

- Lack of procedures to ensure that clinical investigators are aware of their responsibilities, including the reporting requirements listed in 21 CFR 56.108(a)(3) and (4) and 56.108(b). Attachment I of the SOPs, entitled "Investigator Responsibilities," includes a list of materials investigators need to

supply to the IRB. However, neither this attachment nor the body of the SOPs describes a method by which investigators are to be informed of these responsibilities.

- Lack of procedures to ensure that investigators provide the progress reports required for continuing review as well as for IRB actions should study approval lapse. (21 CFR 56.108(a) and 56.109(f))

- Lack of procedures regarding IRB actions to be taken if a study presented as a non-significant risk is determined to be a significant risk study (21 CFR 812.66). It is also suggested that Attachment IV, which discusses IRB review of significant risk/non-significant risk investigational device studies, be referenced in the body of the SOPs where IRB initial review of proposed studies is discussed.

- Inadequate description of a required element for an informed consent document. Item G. of Attachment II, "Elements of Informed Consent," is incomplete. Three contacts are required by 21 CFR 50.25(a)(7): whom to contact (1) for questions pertinent to the research, (2) in the event of research-related injury, and (3) for questions regarding the rights of study subjects. It should also be noted that, while the first two contacts may be the same person, the third contact should be someone who is not associated with the study, possibly an IRB member.

For your information, medical devices that are designated as humanitarian use devices (HUDs) are approved for use via the Humanitarian Device Exemption (HDE). For a facility to use these devices requires IRB oversight. Subpart H. of 21 CFR Part 814 – Premarket Approval of Medical Devices – describes approval and use of HUDs. IRB requirements in this regard are included in 21 CFR 814.124. A copy of Subpart H. is enclosed. Written procedures regarding review of HUDs should be incorporated into IRB SOPs. If your hospital chooses not to allow the use of these devices, it would be helpful to include a statement to that effect instead.

Dr. Hoekstra's response includes proposed changes to the SOPs to include procedures for emergency and/or compassionate use of investigational drugs and devices as well as expedited review, inclusion of a statement regarding determination of the time period for continuing review, and a sample letter to investigators requesting a progress report and/or final report. The response also states that the presence of a membership quorum as well as the details regarding voting will be documented in all IRB minutes and that the [redacted] protocol noted above has already received detailed review by the IRB.

Enclosed with his response, Dr. Hoekstra included copies of the proposed additions to the IRB SOPs as well as a copy of the minutes from the most recent IRB meeting, at which these changes, as well as the [redacted] protocol, were among the items of

business discussed. The response notes that until proposed changes are approved by the hospital's Board of Trustees, all requests for protocol review will be subject to the full IRB review and approval process.

We have reviewed the proposed additions to IRB SOPs. Proposed section H. "Expedited Review Procedure" includes the pertinent issues. In the proposed discussion of emergency and/or compassionate use, item 1 states that emergency use will not be approved for investigational devices, while the remaining items describe a procedure with regard to investigational drugs. For your information, emergency and compassionate use provisions do exist for investigational devices. "Expanded Access to Unapproved Devices," Chapter III of the guidance document, Guidance on IDE Policies and Procedures, describes the necessary conditions for use. This guidance is available at http://www.fda.gov/cdrh/ode/idepolcy.html. A hard copy of Chapter III is also enclosed.

With regard to emergency use of investigational new drugs, 21 CFR 312.36 requires FDA approval, a fact which is not included in your draft procedures. Information regarding emergency use of unapproved drugs and biologics is included in The FDA Information Sheets Guidance for Institutional Review Boards and Clinical Investigators, which can be found at http://www.fda.gov/oc/ohrt/irbs/default.htm.

With regard to the sample letter to an investigator concerning need for a progress report, the wording implies that the required report had not been received when due. As noted above, the SOPs should contain written procedure for ensuring receipt of progress reports needed for continuing review. As part of such a procedure, a letter would issue to investigators prior to the date on which approval would expire, reminding them of the need for a progress report. This letter should specifically note that failure to receive notice of continued approval prior to the expiration date would result in the inability to enter new subjects into the study during any lapse in approval. To enable use of this letter for all studies, including those requiring continuing review more frequently than annually, the letter should refer to required reports as progress reports throughout rather than as annual reports.

The minutes of the August meeting state that, upon review of the protocol for [redacted], IRB members concurred that they had reviewed the full study protocol at the March meeting. However, there is no mention in the response or in any of the enclosures of the study of [redacted] product. Please inform us as to IRB actions taken to assure that review of this study was adequate as well as any action taken or planned should it be confirmed that full review had not taken place.

Within fifteen (15) working days of receipt of this letter, please inform FDA of the additional corrective actions taken to remedy the deficiencies noted above. If additions

and modifications to the SOPs cannot be completed for enclosure with this response, please provide a time table for receipt. Please also provide a copy of IRB meeting minutes for the September meeting of the IRB or of the next scheduled meeting, when available.

Please send all information requested above to the Food and Drug Administration, Center for Devices and Radiological Health, Office of Compliance, Division of Bioresearch Monitoring, Program Enforcement Branch II (HFZ-312), 2098 Gaither Road, Rockville, Maryland 20850, Attention: Jean Toth-Allen, Ph.D. Failure to respond can lead to regulatory actions without further notice, including, as described in 21 CFR 56.120 and 56.121, withholding approval of new studies, directing that no new subjects be added to on-going studies, terminating on-going studies, notifying relevant State and Federal regulatory agencies, and disqualification of the IRB.

A copy of this letter has been sent to FDA's Detroit District Office, 1560 E. Jefferson Avenue, Detroit, Michigan 48207. We request that a copy of your response also be sent to that office.

If you have any questions, feel free to contact Jean Toth-Allen at (301) 594-4723, extension 141.

Sincerely yours,

, RPh, RAC

for Philip J. Frappaolo
Acting Director
Office of Compliance
Center for Devices and Radiological Health

Enclosures